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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Johannes Dirk Anthonie VAN EMBDEN et al.

Serial No. 09/647,596 GROUP 1655

Filed January 16, 2001 Examiner J. Souaya

METHOD OF INTERSTRAIN DIFFERENTIATION OF BACTERIA

RESPONSE

Commissioner for Patents

Washington, D.C. 20231

Sir:

Responsive to the Official Action of July 10, 2001, it is respectfully requested that the above-identified application be re-examined and reconsidered in the manner provided in 37 CFR §1.112, and in the light of the Remarks that follow.

REMARKS

Claims 1-25 were rejected under 35 USC §103 as being obvious in view of VAN EMBDEN et al. WO 95/31569 and Accession numbers M27059 and M27060. That rejection is respectfully traversed.

VAN EMBDEN et al. and Accession numbers M27059 and M27060 fail to render obvious the claimed invention. As the Examiner is aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or knowledge generally available to one of ordinary

skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all of the claimed limitations. The teaching or suggestion to make the claimed combination, and a reasonable expectation of success must both be found in the prior art and not based on Applicants' disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ 2d, 1438 (Fed Cir. 1991).

The VAN EMBDEN et al. document is directed to *Mycobacterium tuberculosis*. While it is noted that because of the success of the method for *Mycobacterium tuberculosis* strain differentiation, the Applicants did use the direct repeat consensus sequence to screen databases for nucleic acid sequences from other microorganisms, nevertheless, it is important to note that no further matches were found. The direct repeat sequence appeared to be unique for the *Mycobacterium tuberculosis* as did their spacer sequences. Despite the negative result after screening with a direct repeat consensus sequence, the Applicants conducted further analysis of known sequences by looking for a pattern in the nucleic acid sequences of other microorganisms reminiscent of the direct repeat spacer pattern in *Mycobacterium tuberculosis*. Quite unexpectedly, the Applicants found by using a specifically designed computer program that such patterns existed in a large number of other microorganisms with a broad range of genera.

The cited documents provide no motivation to combine their respective teachings. A person skilled in the art looking at the teaching of VAN EMBDEN et al. would have realized that the document is specifically directed at *M. tuberculosis* species. No other species, much less an entire genus, is taught or suggested. Thus, the skilled person would have lacked motivation to consider other types of species when faced with the problem of interstrain differentiation. In fact, the Applicant notes that at least 90 publications concerning oligotyping have appeared since the publication of the first VAN EMBDEN et al. patent application. All of these publications are directed to *M. tuberculosis*. Applicants submit that the present patent application is the first directed at oligotyping of microorganisms other than *M. tuberculosis*.

One of ordinary skill in the art would not have had a reasonable expectation of success for achieving the present invention by using the VAN EMBDEN et al. method combined with Accession numbers M27059 and M27060.

It is noted that a large number of categories of microorganisms do not possess the DR pattern of sequences as disclosed by VAN EMBDEN et al. A person skilled in the art when looking at the VAN EMBDEN et al. document would not have had a reasonable expectation of success of finding a similar DR pattern. Furthermore, even if they did attempt this, the chances of them selecting a category of microorganisms in which the DR

pattern is present is quite small. For example, bacteria without a DR locus comprise *Bacillus subtilit, Borrelia burgdorferi sensu stricto, Chlamydia pneumoniae, Chlamydia trachomatis, Haemophilus influenzae, Helicobacter pylori, Mycoplama genitalium, Mycoplasma pneumoniae, Rickettsia prowazekii, Treponema pallidum, Vibrio cholerae 01 El Tor,, Actinobacillus actinomycetemocomitans, Bacillus stearothermophilus, Bordetella bronchiseptica, Bordetella pertussis, Enterococcus faecalis, Klebsiella pneumoniae, Legionella pneumophila, Mycobacterium leprae, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Streptococcus pneumoniae type 4, Synechocystis sp, Thiobacillus ferrooxidans.* The number of organisms without such a sequence would further discourage one of ordinary skill in the art from using the VAN EMBDEN et al. method, much less the additional steps and analysis undertaken by Applicant.

It is respectfully submitted that the Official Action uses hindsight to combine the *E coli* sequence data and the VAN EMBDEN et al. prior patent application. The motivation to combine the two documents according to the Official Action is that as diagnosis of *E coli* is an extremely important subject, the skilled person would use the VAN EMBDEN et al. document to arrive at the use of that method for *E coli*.

However, if the skilled person were to have considered

the move from *Mycobacteria* to other strains, then it is most likely he would have thought of the DR characteristic for other microorganisms in general, and searched for such a sequence in other microorganisms. However, one skilled in the art would not have found them because the identity of the DRs between categories of microorganisms differs. Thus, the identity of DR for microorganisms other than *Mycobacteria* were not known. It is merely with the benefit of hindsight and with the knowledge presented in the present application that the link might seem simple.

The *E coli* DR sequence is not the same as the *M. tuberculosis* DR sequence. The pattern of DR has to be found first in a group of microorganisms, then the identity of the specific DR sequence can be found. Most vitally, there was nothing in the prior art to indicate the DR sequence was not in fact unique to *Mycobacteria* with the different spacers between the DR sequences being that which defined the different *Mycobacterial* strains.

In fact, it is the case that a data base search by VAN EMBDEN et al. was published after their first invention and revealed that there was no homology with the DR sequence and other known sequences at that time. Obviously, not even VAN EMBDEN et al. thought that a pattern of DR-like sequences with differing intermediate spacer sequences was an option for interstrain differentiation of other species. At best, they

thought it was worth a try to see if the DR sequence of *Mycobacterium* resembled anything of a general character. Once this turned out to be negative, the area of research focused elsewhere. It took considerable time, effort and thought to come up with the idea that a pattern of different sequences could be used to distinguish other organism types. Nothing taught or suggested that the structure of a region of DRs and spacers would be present in categories with different identities of DR.

It is also further emphasized that if a person skilled in the art is interested in looking at *E. coli* diagnosis, the skilled person would not look at literature describing *Mycobacteria* diagnosis.

In particular, it is noted that the cited documents fail to provide any links or similarity between *E. coli* or *Mycobacterium*.

Thus, there is no motivation to combine the teachings of the references in the manner proposed in the Official Action, and there is also no reasonable expectation of success in so doing. *E. coli* and *Mycobacteria* are completely different categories of microorganisms. *Mycobacteria* do not belong to the class of *Enterobacteriacae*.

There are many registered *E. coli* sequences to select from as a potential source of diagnosis specific for *E. coli*. One of ordinary skill in the art would not be motivated to use the Patscan program or sequence patterns derived outside

Enterobacteriacae with any reasonable expectation of success.

The pattern as present in *Mycobacteria* do not provide a single indication that a similar pattern is present in other organism categories. There certainly was no motivation to go from *E coli* sequences to *Enterobacteriacae* and beyond to screen for possible diagnostic genomic sequences. The DR pattern of *Mycobacteria* has been known since 1994. The diagnosis of *E coli* has been a problem for a much longer period of time. If the Official Action's supposition that the link between *Mycobacteria* and diagnosis of *E coli* could have been made quickly after the VAN EMBDEN et al. publication came out, one of ordinary skill in the art would have done so. However, it wasn't until the time of the present invention that this problem was solved with this technology.

At best, the Official Action presents an "obvious to try" rationale for a rejection. There is usually an element of "obvious to try" in any research endeavor, since such research is not undertaken with complete blindness but with some semblance of a chance of success. Therefore, "obvious to try" is not a valid test of patentability. *In re Dow* Chemical Co. 837 F2d 469, 5 USPQ 2d 1529 (Fed Cir 1991). As noted above, VAN EMBDEN et al. and Accession numbers M27059 and M27060 fail to provide any motivation to combine the documents. Furthermore, one of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of these two

documents. In fact, the documents even fail to provide a rationale or motivation to take the approach of Applicants. If one of ordinary skill in the art were to have tried to use the method for *Mycobacterium tuberculosis* strain differentiation to determine strain differentiation and other microorganisms, one of ordinary skill in the art would have found no matches. One of ordinary skill in the art would consider this as evidence that the method was specific for *Mycobacterium tuberculosis*. It would not have been obvious to conduct the extensive analysis and inventive thought undertaken by Applicants, much less to achieve the fruit of that work as embodied in the present invention.

It is also noted that the restriction requirement states that a patent to a general method would not be obvious over another bacterium if the sequence of the DR was unknown, or if it was unknown in the prior art that such a bacterium possessed such a direct repeat sequence. In such a case, the two would be patentably distinct. As stated, there are numerous microorganisms requiring interstrain differentiation and thus numerous routes a skilled person could pursue if inclined to look for other species with the same motif, but there are a large number that would not provide a result.

but it was known - cited in D. in May 03

It is accordingly believed that none of the claims are rendered obvious by VAN EMBDEN et al. and accession numbers M27059 and M27060, and that the rejection of the claims should be

withdrawn. Allowance and passage to issue on this basis are respectfully requested.

Respectfully submitted,

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By _____

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January 10, 2002